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Cardiff Road
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1. Your reference

PHM.99-007

2. Patent application number
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9903472.0

17 FEB 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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Shionogi & Co Ltd.
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Japan

Patents ADP number *(if you know it)*

6254007002

7549058001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

CHEMICAL PROCESS

5. Name of your agent *(if you have one)*

DENERLEY, Paul Millington

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Intellectual Property Department
ZENECA Pharmaceuticals
Mereside, Alderley Park
Macclesfield, Cheshire. SK10 4TG
United Kingdom

Patents ADP number *(if you know it)*

1030618002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

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See note (d))

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Description	8
Claim(s)	
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Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
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11. I/We request the grant of a patent on the basis of this application.

On behalf of Shionogi & Co Ltd. Signature [signature] Date 15th Feb 99

On behalf of ZENECA Limited Signature Rynda M. Slack Date 16th Feb 99

12. Name and daytime telephone number of person to contact in the United Kingdom

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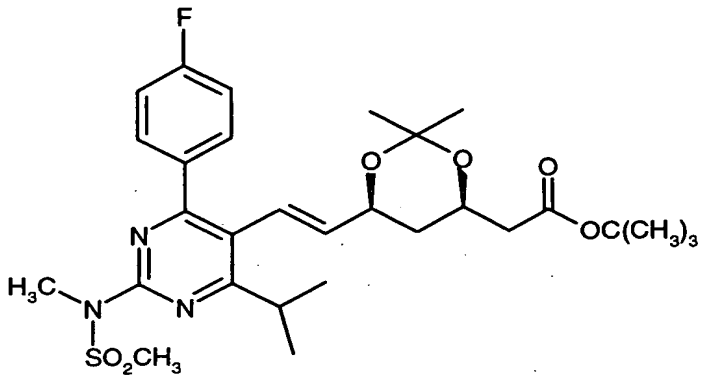
CHEMICAL PROCESS

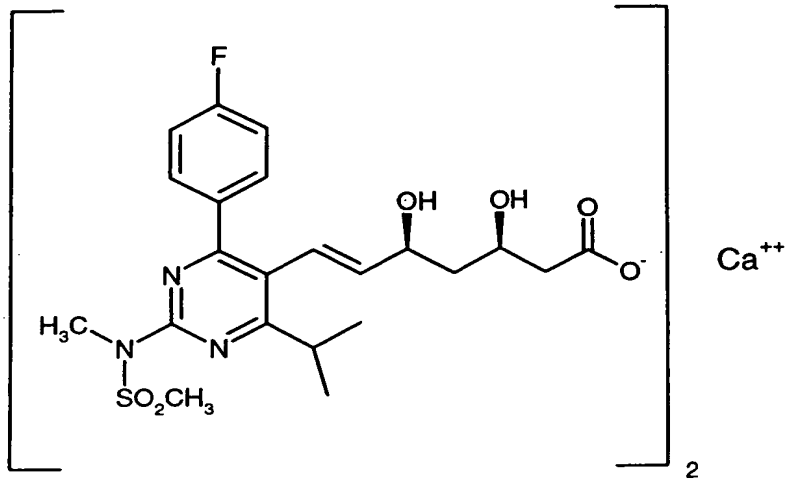
This invention concerns a novel chemical process, and more particularly it concerns a novel chemical process for the manufacture of tert-butyl (6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate of formula I,



Formula I

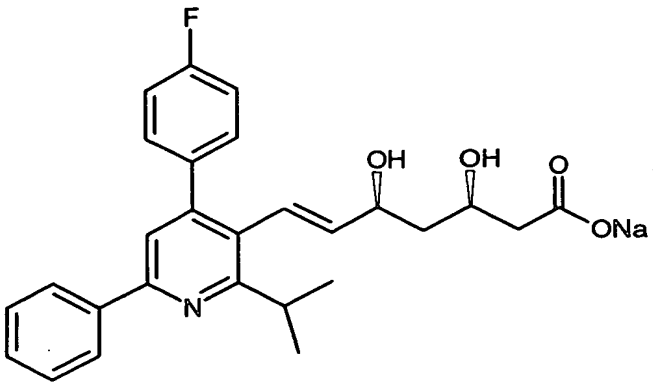
(hereinafter referred to as BEM) which is useful, for example, as a chemical intermediate in the production of a pharmaceutical useful in the treatment of, inter alia, hypercholesterolemia, hyperlipoproteinemia and atherosclerosis. The invention further includes the novel starting material used in said process.

In European Patent Application, Publication No. (EPA) 0521471 is disclosed (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid and its sodium salt and calcium salt (illustrated below)

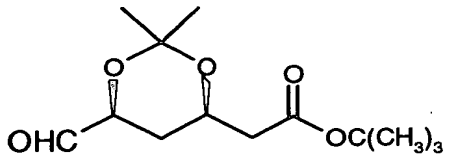


(hereinafter referred to collectively as "The Agent") as inhibitors of HMG CoA reductase.

The preparation of another HMG CoA reductase inhibitor, E,3R,5S-3,5-dihydroxy-7-[4-(4-fluorophenyl)-2-(1-methylethyl)-6-phenylpyridin-3-yl]hept-6-enoic acid sodium salt

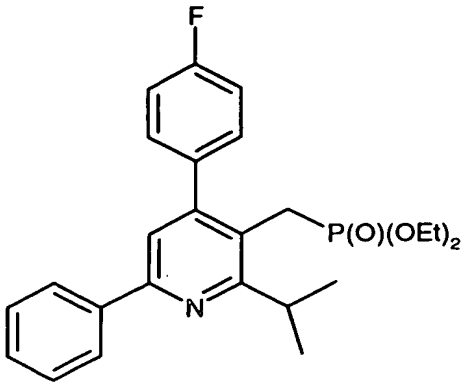


is disclosed in EPA 0319847 (Example 7, parts (a), (b) and (d)), which is obtained by reaction of tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl}acetate of formula II



Formula II

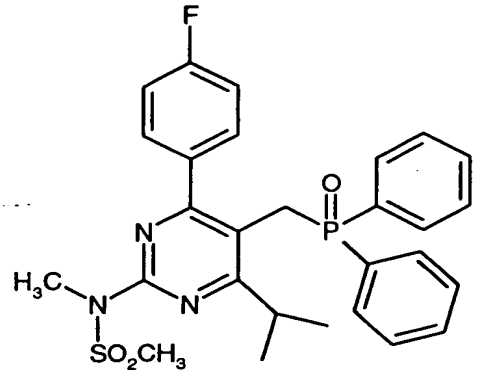
(hereinafter referred to as BFA) with diethyl [4-(4-fluorophenyl)-2-(1-methylethyl)-6-phenylpyridine-3-ylmethyl]phosphonate



in the presence of diisopropylamine and n-butyl lithium, followed by treatment with acid followed by base. By analogy, the Agent may thus be obtained from BEM by treatment with acid (to cleave the acetonide protecting group) followed by base (to cleave the ester) and (as described in EPA 0521471) conversion of the initially formed salt to the free acid or the calcium salt.

We have now discovered a useful and advantageous process for preparing BEM.

According to the invention there is provided a process for preparing BEM (formula I) which comprises reaction of diphenyl [4-(4-fluoropheny)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-ylmethyl] phosphine oxide of formula III



Formula III

(hereinafter referred to as DPPO) with BFA (formula II) in the presence of a strong base.

The process is carried out in a suitable solvent, or mixture of solvents for example, ethereal or aromatic solvents or mixtures thereof. Particularly suitable solvents include, for example, tetrahydrofuran (THF), dimethoxyethane and toluene, or mixtures thereof. Particularly preferred solvents include, for example, THF and THF and toluene.

Suitable bases for use in the process include, for example, amide bases, alkyl metals and metal hydrides. Particular bases include, for example, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium bis(trimethysilyl)amide, butyllithium and sodium hydride. A particularly preferred base is, for example, sodium bis(trimethylsilyl)amide (NaHMDS).

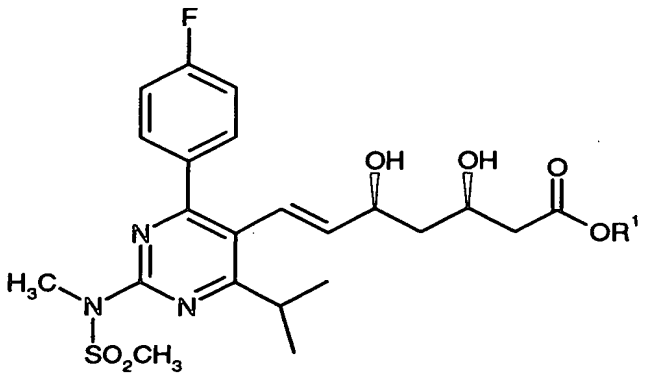
The reaction may be carried out at a temperature in the range of, for example, -20°C to -90°C, for example -40°C to -80°C. A convenient temperature at which to carry out the reaction is, for example, that of a mixture of acetone and solid carbon dioxide (about -75°C).

The process is advantageously carried out with 1.0 to 1.2 equivalents of base (per equivalent of DPPO), such as 1.05 to 1.2 equivalents and preferably 1.05 to 1.12 equivalents. Although BFA can be present in large excess, it is convenient to use 1.0 to 1.35 equivalents (per equivalent of DPPO), and preferably 1.05 to 1.3 equivalents, especially 1.05 to 1.15 equivalents.

The process of the invention provides significantly improved yields and quality of product by comparison to when a corresponding dialkyl phosphonate starting material is used instead of DPPO.

The starting material, DPPO, which is a further aspect of the present invention, may be obtained as described in the Examples hereinafter, starting from an alkyl 2-amino-4-(4-fluorophenyl)-6-isopropylpyrimidin-5-carboxylate, for example the methyl ester which may be obtained as described in Japanese Patent Application No. 06-256318, or the ethyl ester which may be obtained as described in EPA 0521471. BFA may be obtained as described in EPA 0319847 (Example 6).

A further aspect of the present invention is a process for the manufacture of a compound of the formula IV



Formula IV

in which R^1 is hydrogen or a pharmaceutically acceptable cation, which comprises;

(1) reaction of DPPO with BFA in the presence of a strong base (as described above) to give BEM;

(2) cleavage of the dihydroxy (acetonide) protecting group (for example by acid hydrolysis, such as by using HCl in THF or acetonitrile); and

(3) cleavage of the tert-butyl ester group under basic conditions to form a compound of the formula I in which R^1 is a pharmaceutically acceptable cation (for example by using a

solution of a metallic hydroxide in a polar solvent, such as using aqueous sodium hydroxide in ethanol or acetonitrile to form the sodium salt);

optionally followed by neutralisation to give a compound of the formula I in which R^1 is hydrogen;

and/or optionally followed by conversion to another compound of the formula I in which R^1 is a pharmaceutically acceptable cation (for example conversion of the sodium salt to the calcium salt by treatment with a water soluble calcium salt (such as calcium chloride) under aqueous conditions.

Suitable conditions for steps (2), (3) and the subsequent optional steps are analogous to, or the same as, those disclosed in EPA 0521471 and/or EPA 0319847, which are hereby incorporated herein by reference.

The invention is further illustrated, but not limited by the following Examples.

Preparation 1

Preparation of DPPO

A stirred mixture of methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-carboxylate (12.0 g) in toluene (55ml) was cooled to -10°C and diisobutyl aluminium hydride (50 ml of a 1.5M solution in toluene) was added over two hours maintaining the temperature below 0°C. After addition, the mixture was stirred for 30 minutes at 0°C. Methanol (0.64 ml) was added to the mixture maintaining the temperature at 0°C. The mixture was then added over two hours to a stirred mixture of concentrated hydrochloric acid (23.3 ml), water (40.5 ml) and acetonitrile (24 ml) at 40°C, maintaining the temperature of the mixture at 40°C. After addition, the mixture was stirred at 40°C for a further 30 minutes and then purged with nitrogen (to remove any isobutane). The mixture was cooled to 20°C and allowed to stand for 20 minutes. The organic phase was separated and washed with a mixture of concentrated hydrochloric acid (0.7 ml) and water (30 ml). Acetonitrile (24 ml) was added to the organic phase and the mixture washed with a solution of sodium bicarbonate (0.038 g) in water (120 ml).

The organic phase was heated to 40°C, and then from 40°C to 80°C using a nitrogen purge. The mixture was concentrated by distillation at atmospheric pressure, collecting 54 ml of distillate. Acetonitrile (24 ml) was added to the concentrated solution and phosphorus tribromide (1.2 ml) was added with stirring, maintaining the temperature of the mixture at

20°C. After addition, the mixture was stirred at 20°C for 30 minutes. The mixture was added to water (36 ml) over 30 minutes maintaining the temperature at 20°C. The mixture was stirred for 5 minutes and the organic phase separated. The organic phase was washed with a solution of sodium bicarbonate (0.027 g) in water (36 ml), followed by water (36 ml). The organic phase was distilled under reduced pressure until 29 ml of distillates was collected. The mixture was cooled to 60°C and ethyl diphenylphosphinite (7.47 ml) was added. The mixture was stirred at 60°C for 3 hours, then heated to reflux. Toluene (40 ml) was added and the mixture cooled to 0°C over 2 hours. The product was collected by filtration, washed with cold toluene (10 ml) and dried under vacuum at 50°C to give DPPO (14.66 g); ^{1}HNMR ($CDCl_3$, 270 MHz): 7.42 [m, 10H, $P(C_6\underline{H}_5)_2$], 7.12 [m, 2H, Ar-H], 6.92 [m, 2H, Ar-H], 3.92 [d,2H, $C\underline{H}_2P$], 3.51, 3.46 (2 x s, 6H, $NC\underline{H}_3$ $SO_2C\underline{H}_3$], 3.43 [hept., 1H, $C\underline{H}(CH_3)_2$], 1.25 [d, 6H, $CH(C\underline{H}_3)_2$]

Methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino)pyrimidine-5-carboxylate was prepared as follows:

A mixture of methyl 2-amino-4-(4-fluorophenyl)-6-isopropyl-pyrimidine-5-carboxylate (19.0 g), sodium tert-pentoxide (22.95 g) and dimethoxyethane (190 ml) was stirred for 30 minutes at 25°C. The stirred mixture was cooled to -10°C and methanesulfonyl chloride (8.4 ml) was added dropwise, maintaining the temperature of the mixture at -5°C. After 20 minutes, dimethyl sulfate (8.1 ml) was added and the mixture allowed to warm to 25°C. The mixture was stirred for one hour at 25°C and a solution of sodium tert-pentoxide (1.91 g) in dimethoxyethane (10 ml) added. The mixture was stirred for one hour at 25°C. A solution of sodium chloride (13.3 g) in water (133 ml) was added and the mixture was stirred for 10 minutes at 25°C. The mixture was allowed to settle for 15 minutes and the lower aqueous phase was separated and discarded. Water (38 ml) was added to the remaining mixture and the mixture was stirred for 30 minutes at 25°C. The mixture was then heated to obtain a complete solution. The mixture was cooled slowly to 25°C over one hour. The mixture was cooled to 0°C, stirred for one hour, and the suspended solid collected by filtration. The solid was washed with cold (0°C) solution of 50:50 water/dimethoxyethane (20 ml). The solid was dried under vacuum at 60°C to give methyl 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidine-5-carboxylate (19.35 g); ^{1}HNMR (270 MHz, $CDCl_3$): 7.69 (m,2H), 7.14 (m,2H), 3.71, 3.60, 3.51 (3 x s, 9H), 3.20 (m, 1H), 1.32 (d,6H).

Example 1

A mixture of DPPO (19.17 g) and THF (227 ml) were warmed briefly to 40°C until a clear solution had formed then inerted by the sequential application of vacuum and nitrogen (5 cycles). The mixture was immersed in an acetone/CO_2 bath cooling the contents to -75°C. Sodium bis(trimethylsilyl)amide (37.4 ml of 1.0M solution in THF) was added to the reaction mixture over 10 minutes from a pressure equalising dropping funnel maintaining the temperature below -74°C and forming a red solution of the anion. THF (10 ml) was rinsed through the dropping funnel into the mixture and the mixture stirred a further 1 hour at -76°C forming a red suspension. BFA (80 ml of ~13.5% w/w toluene solution) was added in portions to the suspension over 20 minutes from a pressure equalising dropping funnel maintaining the temperature below -73°C. Toluene (20 ml) was rinsed through the dropping funnel into the mixture and the mixture stirred a further 15 minutes at -76°C. The chilling bath was lowered and the suspension allowed to warm to 10°C over 1.5 hours. Glacial acetic acid (3.21 g) in water (15 g) was added in one portion raising the temperature to 18°C and dissolving all solids and the mixture was stirred a further 5 minutes.

The mixture was concentrated by distillation at atmospheric pressure (jacket 110°C) to a temperature of 94°C collecting a total of 274 ml distillates. The concentrated mixture was cooled to 40°C, water (40 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded. Sodium hydrogen carbonate (2.99 g) in water (40 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded. Water (30 ml) was added and the mixture stirred for 5 minutes then allowed to settle for 15 minutes. The lower aqueous phase was discarded.

The organic phase was transferred to a distillation apparatus with toluene (20 ml) and concentrated by distillation at atmospheric pressure (jacket 125-130°C) to a temperature of 116°C collecting 85 ml distillates. Vacuum was applied (400-500 mbar) and a further 16.5 ml distillates collected to a temperature of 111°C. The vacuum was released and the concentrated mixture allowed to cool to 80°C. Warm MeOH (140 ml, 50°C) was added with rapid stirring and the batch allowed to self-cool to 20°C over 30 minutes during which time a solid was deposited. The suspension was further cooled to 2°C for 30 minutes then the solid was collected by filtration on a sinter and pulled as dry as possible. The solid was washed

with cold MeOH (60 ml, 2°C) and again pulled as dry as possible then transferred to a vacuum oven and dried overnight (50°C, 200 mbar); giving BEM (14.01 g, 67.7%).

^{1}H NMR ($CDCl_3$, 270 MHz)

7.65 [m, 2H, Ar-H], 7.09 [m, 2H, Ar-H], 6.52 [dd, 1H, ArCH=CH], 5.47 [dd, 1H, ArCH=CH], 3.57, 3.50 [2 x s, 6H, NCH_3, SO_2CH_3], 3.38 [hept., 1H, Ar-$CHMe_2$], 2.45, 2.30 [2 x dd, 2H, CH_2CO_2tBu], 1.55, 1.13 [dt, dd, 2H, acetonide CH_2], 1.50, 1.40 [2 x s, 6H, acetonide $C(CH_3)_2$], 1.45 [s, 9H, $CO_2C(CH_3)_3$], 1.27 [dd, 6H, $ArCH(CH_3)_2$]

Examples 2-6

The procedure as described in Example 1 was carried out using the ratios of reactants and the temperatures given in Table 1. There was thus obtained BEM in the yields given.

Table 1

Wt DPPO	Temp. (°C)	Eq. NaHMDS	Eq. BFA	BEM Yield
10.00 g	-75	1.12	1.20	69.2%
18.12 g	-75	1.12	1.20	69.6%
12.08 g	-75	1.06	1.26	72.8%
19.17 g	-40	1.05	1.06	56.7%
9.57 g	-90	1.05	1.10	72.0%
9.57 g	-60	1.05	1.10	70.1%